Bupropion

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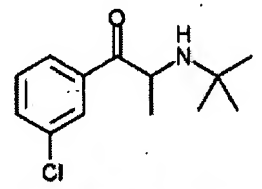
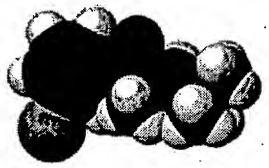
Bupropion (INN; previously known as **amfebutamone**,[1] brand names **Wellbutrin**, **Zyban**, **Budeprion** and **Buproban**) is an atypical antidepressant that acts as a norepinephrine and dopamine reuptake inhibitor, and nicotinic antagonist.[2][3] Bupropion belongs to the chemical class of aminoketones and is similar in structure to the stimulant cathinone, to the anorectic diethylpropion, and to phenethylamines in general.

Initially researched and marketed as an antidepressant, bupropion was subsequently found to be effective as a smoking cessation aid. In 2006 it was the fourth-most prescribed antidepressant in the United States retail market, with more than 21 million prescriptions.[4]

Bupropion lowers seizure threshold and its potential to cause seizures was widely publicized. However, at the





Bupropion

Systematic (IUPAC) name

(±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone

Identifiers

CAS number	34841-39-9 (http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=34841-39-9&rn=1)
ATC code	N07BA02 (http://www.whocc.no/atcddd/indexdatabase/index.php?query=N07BA02)
PubChem	444 (http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=444)
DrugBank	APRD00621 (http://redpoll.pharmacy.ualberta.ca/drugbank/cgi-bin/getCard.cgi?CARD=APRD00621)

Chemical data

Formula	$C_{13}H_{18}ClNO$
Mol. mass	239.74 g/mol

Pharmacokinetic data

recommended dose the risk of seizures is comparable to the one observed for other antidepressants. In contrast to many psychiatric drugs, bupropion does not cause weight gain or sexual dysfunction.

Bioavailability	5 to 20% in animals; no studies in humans
Metabolism	Hepatic—important CYP2B6 and 2D6 involvement
Half life	20 hours
Excretion	Renal (87%), fecal (10%)
Therapeutic considerations	
Pregnancy cat.	B2(AU) C(US)
Legal status	POM(UK) □-only(US)
Routes	Oral

Contents

History

Bupropion was first synthesized by Burroughs Research in 1966, and patented by Burroughs–Wellcome (now GlaxoSmithKline) in 1974. It was approved by the United States Food and Drug Administration (FDA) as an antidepressant on December 30, 1985 and marketed under the name **Wellbutrin**.[5] However, a significant incidence of seizures at the originally recommended dosage (400–600 mg) caused the withdrawal of the drug in 1986. Subsequently, the risk of seizures was found to be highly dose-dependent, and bupropion was re-introduced to the market in 1989 with a maximum recommended dose of 450 mg/day.

In 1996, the FDA approved a sustained-release formulation of

bupropion called **Wellbutrin SR**, intended to be taken twice a day (as compared to three times a day for immediate-release **Wellbutrin**).[6] In 2003 the FDA approved another sustained-release formulation called **Wellbutrin** XL, intended for once-daily dosing. **Wellbutrin SR** and XL are available in the United States in generic form. In **1997**, bupropion was approved by the FDA for use as a smoking cessation aid under the name Zyban.[6] In 2006, **Wellbutrin** XL was similarly approved as a treatment for seasonal affective disorder.[7]

Wellbutrin XL

Therapeutic uses

Depression

Placebo-controlled double-blind clinical studies have confirmed the efficacy of bupropion for clinical depression.[8] Comparative clinical studies demonstrated the equivalency of bupropion and sertraline (Zoloft), fluoxetine (Prozac), paroxetine (Paxil)[9] and escitalopram (Lexapro)[10] as antidepressants. A significantly higher remission rate for bupropion treatment than for venlafaxine (Effexor) was observed in a recent study.[11] Unlike all other antidepressants, except mirtazapine (Remeron) and maprotiline (Ludiomil), bupropion does not cause sexual dysfunction and the occurrence of sexual side effects is not different from placebo.[12][13] Bupropion treatment is not associated with weight gain; on the contrary, at the end of every study comparing bupropion with placebo or other antidepressants the bupropion group had a lower average weight.[14] Bupropion is more effective than SSRIs at improving symptoms of hypersomnia and fatigue in depressed patients.[15]

According to several surveys, the augmentation of a prescribed SSRI with bupropion is the preferred strategy among clinicians when the patient does not respond to the SSRI. Although no placebo-controlled studies of bupropion augmentation have been conducted, open-label trials and case reports generally support this strategy.[16] For example, the combination of bupropion and citalopram (Celexa) was observed to be more effective than switching to another antidepressant. The addition of bupropion to an SSRI (primarily fluoxetine or sertraline) resulted in a significant improvement in 70–80% of patients who had an incomplete response to the first-line antidepressant.[17][18] Bupropion improved ratings of "energy", which had decreased under the influence of the SSRI; also noted were improvements of mood and motivation, and some improvement of cognitive and sexual functions. Sleep quality and anxiety ratings in most cases were unchanged.[18]

Smoking cessation

Bupropion reduces the severity of nicotine cravings and withdrawal symptoms. After a seven-week treatment, 27% of subjects who received bupropion reported that an urge to smoke was a problem, versus 56% of those who received placebo. In the same study, 21% of the bupropion group reported mood swings, versus 32% of the placebo group.[19] The bupropion treatment course lasts for seven to twelve weeks, with the patient halting the use of tobacco about ten days into the course. The efficacy of bupropion is similar to that of nicotine replacement therapy. Bupropion approximately doubles the chance of quitting smoking successfully after three months. One year after the treatment, the odds of sustaining smoking cessation are still 1.5 times higher in the bupropion group than in the placebo group.[20] The combination of bupropion and nicotine appears not to further increase the cessation rate. In a

direct comparison, varenicline (Chantix) showed superior efficacy: after one year, the rate of continuous abstinence was 10% for placebo, 15% for bupropion, and 23% for varenicline.[21] Bupropion slows the weight gain that often occurs in the first weeks after quitting smoking (after seven weeks, the placebo group had an average 2.7 kg increase in weight, versus 1.5 kg for the bupropion group). With time, however, this effect becomes negligible (after 26 weeks, both groups recorded an average 4.8 kg weight gain).[19]

Sexual dysfunction

A large body of evidence exists in favor of treating pharmacologically induced sexual dysfunction with bupropion, though it is not an FDA-approved indication. According to a survey, bupropion is the drug of choice among psychiatrists for the treatment of SSRI-induced sexual dysfunction. 36 percent of responding psychiatrists preferred switching patients with sexual dysfunction to bupropion; however, 43 percent favored the augmentation of the current medication with bupropion.[22] There are studies demonstrating the efficacy of both approaches; improvement of the desire and orgasm components of sexual function were the most often noted. For the augmentation approach, the addition of at least 200 mg/day of bupropion to the SSRI regimen may be necessary to achieve an improvement since the addition of 150 mg/day of bupropion did not produce a statistically significant difference from placebo.[23][24][25][26][27][28]

Several studies have indicated that bupropion also relieves sexual dysfunction in people who do not have depression. In a mixed-gender double-blind study, 63% of subjects on a 12-week course of bupropion rated their condition as improved or much improved, versus 3% of subjects on placebo.[29] Two studies, one of which was placebo-controlled, demonstrated the efficacy of bupropion for women with hypoactive sexual desire,[30][31] resulting in significant improvement of arousal, orgasm and overall satisfaction. Bupropion also showed promise as a treatment for sexual dysfunction caused by chemotherapy for breast cancer[32] and for orgasmic dysfunction.[33] As with the treatment of SSRI-induced sexual disorder, a higher dose of bupropion (300 mg) may be necessary: a randomized study employing a lower dose (150 mg) failed to find a significant difference between bupropion, sexual therapy or combined treatment.[34] Bupropion does not affect any measures of sexual functioning in healthy men.[35]

Obesity

A recent meta-analysis of anti-obesity medications pooled the results of three double-blind, placebo-controlled trials of bupropion. It confirmed the efficacy of bupropion given at 400 mg per day for treating obesity. Over a period of 6 to 12 months, weight loss in the bupropion group (4.4 kg, 10 lb) was significantly greater than in the placebo group (1.7 kg, 4 lb). The same review found the differences in weight loss between bupropion and other established weight-loss medications, such as sibutramine, orlistat and diethylpropion, to be statistically insignificant.[36]

Attention-Deficit Hyperactivity Disorder

Although attention-deficit hyperactivity disorder (ADHD) is not an approved indication, bupropion was found to be effective for adult ADHD.[37] There have been many positive case studies and other uncontrolled clinical studies of bupropion for ADHD in minors.[38] However, in the largest to date double-blind study, which was conducted by GlaxoSmithKline, the results were inconclusive.

Aggression and hyperactivity as rated by the children's teachers were significantly improved in comparison to placebo; in contrast, parents and clinicians could not distinguish between the effects of bupropion and placebo.[38] The 2007 guideline on the ADHD treatment from American Academy of Child and Adolescent Psychiatry notes that the evidence for bupropion is "far weaker" than for the FDA-approved treatments. Its effect may also be "considerably less than of the approved agents... Thus it may be prudent for the clinician to recommend a trial of behavior therapy at this point, before moving to these second-line agents."[39] Similarly, the 2006 guideline from the Texas Department of State Health Services recommends considering bupropion or a tricyclic antidepressant as a fourth-line treatment after trying two different stimulants and atomoxetine (Strattera).[40][41]

A study of prophylactic bupropion for the prevention of smoking among teenagers with ADHD yielded unexpected results. The teenagers taking bupropion were twice more likely (close to statistical significance) to begin smoking than the teenagers in the placebo group. At the same time, the sub-group of patients taking stimulants in addition to bupropion or placebo had a five times lower risk of smoking initiation.[42]

Other uses

Bupropion is used for the prevention of seasonal affective disorder,[43] and has been approved by the FDA for the latter indication.[44] There is considerable disagreement regarding whether the addition of an antidepressant, including bupropion, to a mood stabilizer in patients with bipolar depression is useful.[45][46][47]

No properly controlled double-blind studies of bupropion for Parkinson's disease have been conducted. A small 1984 study funded by bupropion's manufacturer found that addition of bupropion to carbidopa or levodopa improved Parkinson's symptoms in ten out of twenty patients; however, the side effects, particularly nausea and vomiting, were frequent.[48] The American Psychiatric Association notes that, "there is no evidence favoring any particular antidepressant medication from the standpoint of therapeutic efficacy in patients with Parkinson's disease complicated by major depressive disorder."[49]

Contraindications

GlaxoSmithKline advises that bupropion should not be prescribed to individuals with epilepsy or other conditions that lower the seizure threshold, such as alcohol or benzodiazepine discontinuation, anorexia nervosa, bulimia, or active brain tumors. It should be avoided in individuals who are also taking MAO inhibitors (MAOIs). When switching from MAOIs to bupropion, it is important to include a washout period of about two weeks between the medications.[50] The prescribing information approved by the FDA recommends that caution should be exercised when treating patients with liver damage, severe kidney disease, and severe hypertension, as well as in pediatric patients, adolescents and young adults due to the increased risk of suicidal ideation.[50]

According to a retrospective case series published in 1993, bupropion treatment may exacerbate tics in children with co-occurring ADHD and Tourette syndrome.[51] No further research of this side effect has been conducted.

Risk of suicide

The FDA requires all antidepressants, including bupropion, to carry a black box warning stating that antidepressants may increase the risk of suicide in persons younger than 25. This warning is based on a statistical analysis conducted by the FDA which found a 2-fold increase of the suicidal ideation and behavior in children and adolescents, and 1.5-fold increase of suicidality in the 18–24 age group.[52]

Suicidal ideation and behavior in clinical trials are rare. For the above analysis, the FDA combined the results of 295 trials of 11 antidepressants for psychiatric indications in order to obtain statistically significant results. Considered separately, bupropion and nine other antidepressants were not statistically different from placebo. Only fluoxetine caused a significant decrease in suicidal ideation.[52]

Suicidal behavior is even less likely when bupropion is prescribed for smoking cessation. According to a Cochrane Database review, there have been four suicides per one million prescriptions and one case of suicidal ideation per ten thousand prescriptions of bupropion for smoking cessation in the UK. The review concludes, "Although some suicides and deaths while taking bupropion have been reported, thus far there is insufficient evidence to suggest they were caused by bupropion."[53]

Adverse effects

The common adverse effects associated with 12-hour sustained-release bupropion (with the greatest difference from placebo) are dry mouth (17% vs 7% for placebo), nausea (13% vs 8% for placebo), insomnia (11% vs 6% for placebo), tremor (6% vs 1% for placebo), excessive sweating (6% vs 2% for placebo) and tinnitus (6% vs 2% for placebo). Those that most often resulted in interruption of the treatment in the same trial were rash (2.4%) and nausea (0.8%). The development of mild to moderate skin rashes is associated with sensitivity to dye components within the pill coating. This can often be alleviated simply by prescribing a differently colored pill.[50]

Seizure is the most controversial side effect of bupropion, and was responsible for its initial withdrawal from the market. The risk of seizure is highly dose-dependent: 0.1% at 100–300 mg of bupropion, 0.4% at 300–450 mg, and 2% at 600 mg. For comparison, the incidence of the first unprovoked seizure in the general population is 0.07–0.09%. The risk of seizure for other antidepressants is as follows: 0.1–0.6% for imipramine, depending on dosage; 0–0.06% for amitriptyline, depending on dosage; 0.5% for clomipramine; 0.4% for maprotiline; and 0.2% for fluoxetine and fluvoxamine.[54] Experiments on mice indicate that increased susceptibility to seizure is a general side effect of chronically using antidepressants that inhibit norepinephrine transporter, such as imipramine, desipramine and reboxetine.[55] Clinical depression itself was reported to increase the occurrence of seizures two-to-seven-fold compared with the general population; in this light, the above statistics could indicate that low to moderate doses of antidepressants, including bupropion, may actually have an anti-convulsive action.[56]

There is evidence of several neuropsychiatric symptoms associated with bupropion in patients with depression, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms are reduced or eliminated by decreasing the dose or ceasing treatment. The prescribing information notes that "it is generally believed (though not established in controlled trials)" that, should an episode of depression actually be the first presentation of bipolar disorder, treating it with antidepressants, including bupropion, may precipitate a manic episode.[50] More recent data indicate that the addition of newer antidepressants, including bupropion, to a mood stabilizer does not cause the switch to mania more often than the addition of placebo.[46] Moreover,

when added to a mood stabilizer, bupropion and sertraline had a twice lower switch risk than venlafaxine.[57]

The prescribing information notes that hypertension, sometimes severe, was observed in some patients, both with and without pre-existing hypertension. The frequency of this adverse effect was under 1% and not significantly higher than that found with placebo.[50] In a group of cardiac patients with depression, high doses of bupropion (400–500 mg/day) caused a rise in supine blood pressure but had no effect on pulse rate.[58] No statistically significant changes in blood pressure or heart rate occurred in patients with or without heart conditions at a lower dose of 300 mg/day.[59] In a study of bupropion for ADHD, a rise of systolic blood pressure by 6 mm Hg and of heart rate by 7 beats per minute (both statistically significant) were observed.[60] A study of smokers hospitalized for heart disease found a 1.5-fold increase (close to being statistically significant) in subsequent cardiovascular events in the bupropion group, compared with the placebo group, but found no difference in blood pressure.[61] Although the cardiovascular side effects of bupropion appear to be mild, it cannot be recommended for patients with heart disease, since the safety comparison with SSRIs (such as sertraline and fluoxetine, which may have a preventative effect after a myocardial infarction[62]) is not in its favor.

In the UK, more than 7,600 reports of suspected adverse reactions were collected in the first two years after bupropion's approval by the MHRA as part of the Yellow Card Scheme, which monitored side effects. Approximately 540,000 people were treated with bupropion for smoking cessation during that period. The MHRA received 60 reports of "*suspected* [emphasis MHRA's] adverse reactions to Zyban which had a fatal outcome". The agency concluded that "in the majority of cases the individual's underlying condition may provide an alternative explanation."[63] This is consistent with a large, 9,300-patient safety study that showed that the mortality of smokers taking bupropion is not higher than the natural mortality of smokers of the same age.[64]

Other isolated adverse affects have been reported. Three cases of liver toxicity have been described in the literature,[65] a very low incidence given the widespread use of the drug. A single case of clitoral priapism (clitorism) has been reported in the literature.[66]

Overdose

Overdose of bupropion results in significant clinical effects in over one-third of cases.[67] The most common symptoms include sinus tachycardia, hypertension, drowsiness, lethargy, agitation, nausea and vomiting, and in particular delirium and seizures.[67][68][69] Less commonly additional symptoms include auditory and visual hallucinations,[70] coma,[69] and ECG changes such as conduction disturbance or arrhythmia.[71][72][73]

In the majority of childhood exploratory ingestions involving one or two tablets, children will remain asymptomatic.[74][75] In teenagers and adults seizures are more commonly observed with the seizure rate increasing tenfold with doses of 600 mg daily.[76] One overdose study suggested a dose-dependent relationship with seizures; patients ingesting more than 4.5 g were likely to have a seizure and nearly all patients ingesting more than 9 g had a seizure.[67]

There is no specific antidote for bupropion; treatment is supportive, and focuses on maintaining airway patency and controlling seizures with high dose intravenous benzodiazepines or barbiturates if seizures are refractory to benzodiazepines.[68] Gastric decontamination may be of little benefit given the risk of seizures and aspiration[68] but activated charcoal is recommended,[67] additionally whole bowel

irrigation should be undertaken in those ingesting sustained release formulations.[68] Toxic effects may be delayed in onset, with seizures developing as late as 32 hours,[68] subsequently patients should undergo electroencephalographic monitoring for 48 hours.[50]

Bupropion overdose rarely results in death, although cases have been reported.[71][77][78] Fatalities are typically associated with large overdosage and related to metabolic acidosis and hypoxia as complications of status epilepticus with associated cardiorespiratory arrest.[79]

Mechanism of action

Bupropion is a dopamine and norepinephrine reuptake inhibitor.[80] It is about twice as potent an inhibitor of dopamine reuptake than of norepinephrine reuptake. As bupropion is rapidly converted in the body into several metabolites with differing activity, its action cannot be understood without reference to its metabolism. The occupancy of dopamine transporter (DAT) by bupropion and its metabolites in the human brain as measured by positron emission tomography was 6–22% in an independent study[81] and 12–35% according to GlaxoSmithKline researchers.[82] Based on analogy with serotonin reuptake inhibitors, higher than 50% inhibition of DAT would be needed for the dopamine reuptake mechanism to be a major mechanism of the drug's action. Bupropion does not inhibit monoamine oxidase or serotonin reuptake. However, it has been shown to indirectly enhance the firing of serotonergic neurons, via activation of downstream norepinephrine flow. Bupropion has also been shown to act as a noncompetitive α3β4 nicotinic antagonist.[83] The degree of inhibition of α3β4 receptors correlates well with the decrease in self-administration of morphine and metamphetamine in rats,[84] and may be relevant to the effect of bupropion on nicotine addiction.

Pharmacokinetics

Bupropion is metabolized in the liver. It has several active metabolites: *R,R*-hydroxybupropion, *S,S*-hydroxybupropion, *threo*-hydrobupropion and *erythro*-hydrobupropion, which are further metabolized to inactive metabolites and eliminated through excretion into the urine. Pharmacological data on bupropion and its metabolites are presented in Table 1. Bupropion is known to weakly inhibit the α_1 adrenaline receptor, with a 14% potency of its dopamine uptake inhibition, and the histamine H_1 receptor, with a 9% potency.[85]

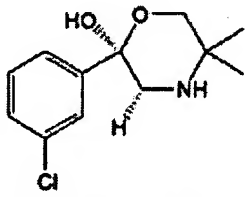
The biological activity of bupropion can be attributed to a significant degree to its active metabolites, in particular to *S,S*-hydroxybupropion. GlaxoSmithKline developed this metabolite as a separate drug called radafaxine,[86] but discontinued development in 2006 due to "an unfavourable risk/benefit assessment".[87]

Bupropion is metabolized to hydroxybupropion by CYP2B6, an isoenzyme of the cytochrome P450 system. Alcohol causes an increase of CYP2B6 in the liver, and persons with a history of alcohol use metabolize bupropion faster. The mechanism of formation of *erythro*-hydrobupropion and *threo*-hydrobupropion has not been studied but is probably mediated by one of the carbonyl reductase enzymes. The metabolism of bupropion is highly variable: the effective doses of bupropion received by persons who ingest the same amount of the drug may differ by as much as 5.5 times (and the half-life from 3 to 16 hours), and of hydroxybupropion by as much as 7.5 times (and the half-life from 12 to 38 hours).[88][89]

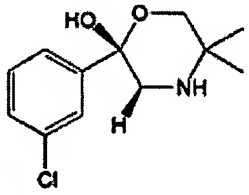
There are significant interspecies differences in the metabolism of bupropion, with guinea pigs' metabolism of the drug being closest to that of humans.[90] Particular caution is needed when extrapolating the results of experiments on rats to humans since hydroxybupropion, the main metabolite of bupropion in humans, is absent in rats.[91]

Due to the high variability of bupropion's pharmacokinetics, the recommended starting dose of 150 mg for 2.5% of the patients may be equivalent to 450–500 mg for an average patient. Based on this, some researchers have advocated monitoring of the blood level of bupropion and hydroxybupropion.[92] Because this is infeasible in routine clinical practice, a lower starting dose of 75 mg may be considered.

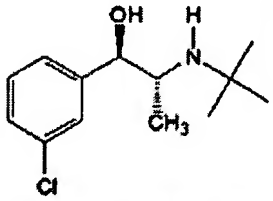
There have been two reported cases of false-positive urine amphetamine tests in persons taking bupropion. Bupropion metabolites *erythro*-hydrobupropion and *threo*-hydrobupropion, which have a phenethylamine structure resembling amphetamine are likely to have been responsible for this reaction. More specific follow-up tests were negative.[93][94]



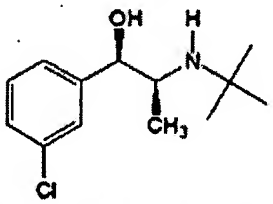
R,R-hydroxybupriopion



S,S-hydroxybupriopion
(Radafaxine)



(+)-*threo*-hydrobupropion
(R,R-hydrobupropion)



erythro-hydrobupropion
(R,S-hydrobupropion)

Important metabolites of bupropion.

DA = dopamine; NE = norepinephrine; Ser = serotonin.

Interactions

Since bupropion is metabolized to hydroxybupropion by the CYP2B6 enzyme, drug interactions with CYP2B6 inhibitors are possible: this includes medications like paroxetine, sertraline, norfluoxetine (the active metabolite of fluoxetine), diazepam, clopidogrel, and orphenadrine. The expected result is the increase of bupropion and decrease of hydroxybupropion blood concentration. The reverse effect (decrease of bupropion and increase of hydroxybupropion) can be expected with CYP2B6 inducers, such as carbamazepine, clotrimazole, rifampicin, ritonavir, St John's Wort and others.[99]

Hydroxybupropion (but not bupropion) is itself an inhibitor of CYP2D6, as well as a substrate of that enzyme. A significant increase in the concentration of some drugs metabolized by CYP2D6 (venlafaxine, desipramine and dextromethorphan, but not fluoxetine or paroxetine) has been observed when they are taken with bupropion.[99][100]

Bupropion lowers the seizure threshold; accordingly, extreme care should be taken when prescribing bupropion with other medications that also lower it, such as antipsychotics, theophylline, steroids, and some tricyclic antidepressants.[50] Its combination with nicotine replacement therapies can elevate blood pressure; since this combination is no more effective than either a nicotine patch or bupropion alone, it is not recommended.

The prescribing information recommends minimizing the use of alcohol, since in rare cases bupropion reduces alcohol tolerance, and because the excessive use of alcohol may lower the seizure threshold.[50] A small study conducted by GlaxoSmithKline indicated that bupropion (100 mg) may counteract the subjective effects of small doses of alcohol (16–32 mL, slightly less than 1–2 standard US drinks). The volunteers reported feeling more sober and clear-headed and less sedated. Bupropion also reduced the detrimental effect of alcohol on auditory vigilance. The combination of bupropion (100 mg) and two drinks of alcohol increased heart rate by six beats per minute, a statistically significant increase.[101]

Availability

Brand-name and generic bupropion tablets are available in three forms: immediate release (**Wellbutrin**), sustained release (**Wellbutrin SR**), and extended release (**Wellbutrin** XL or XR). "Sustained release" and "extended release" are generally interchangeable terms, but in this case **Wellbutrin SR** is intended for twice-daily dosing and **Wellbutrin** XL is intended for once-daily dosing. Not all generics have retained this naming scheme, and the United States Pharmacopeia requires all prolonged-release drug formulations (including generics for **Wellbutrin SR**) to be labeled "extended release", which has caused confusion and medication errors.[102][103] According to GlaxoSmithKline, a 150 mg **Wellbutrin SR** tablet can be split in two and retain its sustained-release characteristics.[104]

In the United Kingdom and Australia, bupropion was approved as a smoking cessation aid in 2000, but has not been approved for the treatment of depression.[105][106] Zyban is available via prescription in the UK only with a letter from a smoking cessation clinic to the patient's physician confirming that he or she is a heavy smoker who has not benefited from nicotine replacement therapies.

In France, marketing authorization was granted on August 3, 2001, also solely as a smoking cessation aid, and with a maximum daily dose of 300 mg;[107] only sustained-release bupropion is available. Bupropion was granted a licence for use in adults with major depression in the Netherlands in early 2007, with GlaxoSmithKline expecting subsequent approval in other European countries.[108]

Bupropion is available internationally under the following brand names:

- Elontril (Germany)
- Odranal (Colombia)
- Quomen (Thailand)
- Well (Korea)
- **Wellbutrin**, **Wellbutrin SR**, **Wellbutrin** XL, Zyban (United States, Canada)
- **Wellbutrin** XR (Netherlands)
- Zetron (Brazil)
- Zyban LP (France)
- Zyban Sustained Release (Australia)
- Zyban **SR** (Poland, United Kingdom)
- Zylexx **SR** (Pakistan)

Abuse liability

According to the US government classification of psychiatric medications, bupropion is "non-abusable"[109] or has low abuse potential.[110] In animal studies, however, squirrel monkeys[111] and rats[112] maintained the intravenous self-administration of bupropion, which may indicate abuse potential—though important differences of bupropion metabolism in rats and humans make any extrapolations invalid.

Two studies on drug abusers indicated that the subjective effects of bupropion are markedly different from those of amphetamine.[113][114] Healthy volunteers trained to discriminate amphetamine and placebo recognized bupropion (400 mg) as amphetamine 20% of the time, compared to 10% for placebo and 75% for methylphenidate (20 mg). They also reported feeling alert, vigorous, elated and energetic, reflecting the general stimulating properties of bupropion. In contrast to amphetamine and methylphenidate, there was no feeling of "liking the drug" and no desire to take it again.[115] A comparison of bupropion **SR** (150 mg) and caffeine (178 mg) indicated that caffeine may have higher abuse liability since it resulted in more reports of pleasant feelings and a "high" than bupropion.[116]

There have been only three reports of bupropion abuse in the literature. All three cases described teenagers crushing and insufflating (snorting) the drug, one of them resulting in seizures.[117] An article on medication abuse in prisons mentions bupropion as one of the psychotropic medications commonly abused by inmates.[118]

References

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External links

- Wellbutrin official website (http://www.wellbutrin-xl.com/)
- Bupropion (http://www.dmoz.org/Health/Pharmacy/Drugs_and_Medications/B/Bupropion/) at the Open Directory Project
- Wellbutrin Pharmacology, Pharmacokinetics, Studies, Metabolism - Bupropion - RxList Monograp (http://www.rxlist.com/cgi/generic/buprop_cp.htm)
- NAMI Wellbutrin (http://www.nami.org/Template.cfm?Section=About_Medications&template=/ContentManagement/ContentDisplay.cfm&ContentID=7
- Bupropion article from mentalhealth.com (http://www.mentalhealth.com/drug/p30-b04.html)
- A Review of the Neuropharmacology of Bupropion, a Dual Norepinephrine and Dopamine Reupta Inhibitor (http://www.psychiatrist.com/pcc/pccpdf/v06n04/v06n0403.pdf)PDF (94.7 KiB)

Retrieved from "http://en.wikipedia.org/wiki/Bupropion"

Categories: Antidepressants | Dopamine reuptake inhibitors | Amphetamines | Stimulants | Phenethylamir

FAQ's

Description of Medical Areas

About the FDA Approved Listings

Drugs Approved by the FDA

Drug Name: Zyban Sustained-Release Tablets

The following information is obtained from various newswires, published medical journal articles, and medical conference presentations.

Company: GlaxoWellcome
Approval Status: Approved May 1997
Treatment for: smoking cessation

General Information

Zyban Sustained-Release Tablets have been approved for use as a smoking cessation treatment. It is the first nicotine-free prescription medicine available. It is also the first smoking cessation treatment available in tablet form. Zyban will be available by prescription approximately July 1997.

In addition, the medication includes a patient support program Zyban Advantage Plan--at no additional patient cost. The plan provides additional support and specific smoking cessation techniques.

Clinical Results

The effectiveness of Zyban as an aid to smoking cessation was demonstrated in two placebo-controlled, double-blind studies. Over 1,500 chronic smokers who smoked at least 15 cigarettes a day participated in these studies. In one study, Zyban was compared to placebo; in the other study, Zyban was evaluated versus placebo, a nicotine patch (Habitrol (R)(1)), and in combination with the patch. In both studies, all patients received brief individual smoking cessation counseling.

In the study involving the patch, patients treated with Zyban had significantly higher 4-week quit rates than those treated with the patch. Patients treated with the combination of Zyban and the patch had significantly higher quit rates than those treated with the patch alone. Quit rates with combination therapy, while higher, were not statistically higher than quit rates with Zyban alone. The 4-week quit rates from this study were 23% for placebo; 36% for the patch; 49% for Zyban; and 58% for the combination of Zyban and the patch.

For many patients, treatment with Zyban reduced withdrawal symptoms.

Withdrawal symptoms showing the most pronounced reductions were: irritability, frustration or anger, anxiety, difficulty concentrating, restlessness, and depressed mood or negative affect. In patients treated with Zyban there was also evidence of a reduction in craving for cigarettes or urge to smoke.

Side Effects

The most common side effects associated with the use of Zyban are dry mouth and insomnia. These side effects are reported to be generally mild, and often disappear after a few weeks. The use of Zyban is also associated with a dose-dependent risk of seizure. Higher than recommended doses should not be prescribed.

Zyban should not be used in people who are already taking Wellbutrin(R), Wellbutrin(R) SR, or any other medication that contains bupropion. It should also not be used in people who are taking or have recently taken a monoamine oxidase inhibitor (MAOI). Zyban should not be used in patients with a seizure disorder who have a history, or are currently diagnosed with bulimia or anorexia nervosa.

Mechanism of Action

Currently, it is unclear how Zyban works. However, it does affect noradrenergic and/or dopaminergic mechanisms in the brain, which have been implicated as pathways of nictotine addiction.

Drug listing last updated on June 29, 2004

PAC> **019389**

Patient Resources: [Trial Listing] [Notification Services] [Drug Directories]
[About Clinical Research] [Patient Resources] [Patient Bookstore]
Professional Resources: [Research Center Profiles] [Industry Provider Profiles] [Jobs in Clinical Resear
[Industry News] [Professional Resources] [Professional Bookstore]
General: [Search] [Site Map] [Your Privacy] [CW World] [Home]

Use of FDA-Approved Pharmacologic Treatments for Tobacco Dependence --- United States, 1984--1998

from Morbidity & Mortality Weekly Report

Report

Of the estimated 48 million adult smokers in the United States, approximately 16 million attempt to stop smoking cigarettes for at least 24 hours annually; another 2--3 million attempt to stop but cannot abstain for 24 hours [1]. However, 1.2 million (2.5%) persons stop smoking each year [2]. Although behavioral and pharmacologic methods increase abstinence rates [3], most cessation attempts are undertaken without the benefit of treatment [4]. In 1984, the Food and Drug Administration (FDA) approved the first pharmacologic aid for smoking cessation, nicotine gum. Since then, other treatments have become available. This study estimates the number of quit attempts using FDA-approved pharmacologic aids during 1984--1998. The study results indicate that product use has changed over this period and that the availability of over-the-counter (OTC) products and the introduction of new products have increased pharmacologically assisted quit attempts.

Information about the sales of prescription smoking-cessation products was obtained from the National Data Corporation* (NDC) by the Source Prescription Audit (SPA). By 1991, the pharmacy sample included approximately 25,000 pharmacies and 75 million prescriptions filled nationally each month; by 1998, sales data included 34,000 pharmacies and 150 million prescriptions covering approximately 66% of the total number of prescriptions in the United States. The total number of prescriptions was obtained through an agreement with PCS Health Systems, Inc., which provides electronic claims services for almost every retail pharmacy.

Information about the sale of OTC products was based on data gathered by ACNielsen, a marketing research organization, that tallied purchases using an electronic Universal Product Code (UPC) scanner. Scanner data were collected from a sample of 10,000 outlets located primarily in the top 50 U.S. markets. Purchases from retail outlets without scanner technology were estimated from a sample of those stores. The combined sample was weighted to estimate total purchases from all outlets. Purchase data from a representative panel of 40,000 households were used to estimate the proportion of unit sales of OTC nicotine replacement therapy (NRT) products representing new uses or quit attempts. The panel of households used a UPC scanner placed in their home to scan purchases after shopping. A new use or quit attempt was counted when an OTC product appeared for the first time in a household's data during a particular calendar year. ACNielsen retail volume estimates were adjusted to project the total number of new OTC uses based on these data.

In 1992, the availability of prescription nicotine patches increased the estimated number of pharmacologically assisted quit attempts per year from 1--2 million to approximately 7 million (Figure 1). The estimated number of quit attempts then decreased, ranging from 2 million to 3 million during 1993--1995, but increased to approximately 6 million in 1996, coinciding with the availability of nicotine gum and the nicotine patch as OTC products. The estimated number of pharmacologically assisted quit attempts increased in 1997 and remained at that level in 1998. By 1998, the nicotine patch accounted for 49% of the pharmacologically assisted quit attempts, nicotine gum, 28%; Zyban, 21%; and nicotine inhaler and nasal spray, <3%. To examine the relation of use to medication availability, data were aggregated into periods marked by the introduction of new treatments and changes in the regulatory status of treatments. In general, use has increased over time as availability improved, and to a lesser extent as new products were introduced. For example, the number of average monthly estimated quit attempts was 642,000 during May 1996--May 1997 when nicotine gum and patches became available OTC, compared with 259,000 during January 1993--April 1996. The introduction of Zyban increased average monthly estimated quit attempts to 708,000.

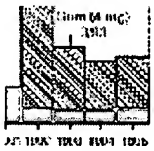

Figure 1. (click image to zoom)

Reported by: SL Burton, SmithKline Beecham Consumer Healthcare, Pittsburgh, Pennsylvania. JG Gitchell, Pinney Associates, Bethesda, Maryland.† S Shiffman, Smoking Research Group, Dept of Psychology, Univ of Pittsburgh, and Pinney Associates, Pittsburgh, Pennsylvania. Epidemiology Br, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, CDC.

Editorial Note

This report suggests that providing more pharmacologic options to smokers can increase the number of treatment-assisted quit attempts. The two largest increases in medication use occurred when prescription patches were introduced in 1992 and when nicotine gum and patches became available without a prescription. The initial increase in use that followed patch introduction was not maintained. A peak in consumer demand outstripped supply, making patches difficult to purchase. The shortage combined with possible smoker and physician disappointment in the patch's efficacy may have caused a decline during the next 3 years to one third of the 1992 volume. The increased sales coinciding with OTC marketing of patches and gum have been sustained for several years. This volume may be attributable to smokers' more realistic expectations about the role of NRT in quit efforts. New NRT and non-NRT products have been approved since 1996. The introduction of the non-nicotine prescription medication, Zyban, appears to have increased modestly the number of pharmacologically assisted cessation attempts. The introduction of two new prescription forms of NRT (i.e., nicotine nasal spray and oral inhaler) have had almost no impact on treatment use. This lack of effect may have occurred because of poor acceptance of these forms, poor promotion, or limits on the demand for and penetration of prescription NRT products when NRT is available without a prescription.

Potential barriers to use of tobacco treatment medications include concerns about the safety and cost of the treatments. FDA has approved all of these treatments as safe and effective, and those approved for OTC availability were deemed sufficiently safe not to require physician screening or intervention. Treatment guidelines recommend that treatment of tobacco use be an insured medical benefit [3]. A recent study in a health plan demonstrated that decreasing the costs of treatment increased use of treatment and the number of persons who quit smoking [5]. This is important because the prevalence of smoking is higher among persons of low socioeconomic status; access to these treatments must be assured in these populations.

The results of this study are subject to at least three limitations. First, estimates of use are based on sales data, prescription audits, and home scanning of purchases rather than direct questioning of users. It is not possible to determine whether a particular purchase represents a new quit attempt or the use of a product as a substitute for smoking in places where smoking is not allowed. In addition, the accuracy of pharmacy data may have improved over time as coverage increased, resulting in

more accurate estimates for recent years. Second, prescription and OTC data are estimated by different methods and data sources. Prescription data may overestimate quit attempts because they may not adequately track successive prescriptions within a quit attempt. OTC data may underestimate quit attempts because they reflect only one quit attempt per household per year. Therefore, actual differences between prescription and OTC products may be greater than reported in these estimates. Finally, although shifts in use corresponded to major shifts in availability and marketing of medications, this study did not examine use in relation to concurrent events such as changes in smoking policies or legislation, higher cigarette prices, increased awareness of health issues, or shifts in population attitudes and beliefs.

The health benefits of quitting are substantial and are realized within a few years of quitting [6]. Promotion of quitting is vital to reduce death and disease caused by tobacco, and recommended levels of resources to be applied to treatment of tobacco dependence have been developed and disseminated by CDC [7]. In addition, increased cessation rates will be essential to achieve the *Healthy People 2010* objectives, [8] and the American Cancer Society's Challenge Goals for the Year 2015 [9]. Public health authorities, including the World Health Organization, have called for an increased focus on the treatment of tobacco dependence to reduce tobacco-caused death and disease. Pharmacologic interventions double success rates [3]; however, these interventions must be used for their effects to be observed. Data from this report suggest that increasing the number of treatment options and the availability of pharmacologic products increases use of these treatments.

* Use of trade names and commercial sources is for identification only and does not imply endorsement by CDC or the U.S. Department of Health and Human Services.

† Pinney Associates provides consulting services to SmithKline Beecham, which develops and markets smoking cessation medications.

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MMWR 49(29), 2000.

Orexigen(OREX)

123Jump Rating:	- Value Gap	**Underwriters:**	Merrill Lynch & Co. J. P. Morgan & Co.
Status:	Priced		
Address:	12841 High Bluff Drive, Suite 160 San Diego CA 92130	**FiledDate:**	12/19/2006
		Filed Price Range ($):	$11.00-13.00
Telephone:	858- 480-2420	**Filed Offer Amount ($ Million):**	$86.00
Fax:		**Shares Offered (Millions):**	6.00
Websites:	www.orexigen.com	**Shares Outstanding (Millions):**	24.86
Management:	Gary Tollefson, CEO	**IPO Date:**	04/25/2007
		Final Offer Price ($):	$12.00
Industry:	Healthcare	**Final Offer Size (Millions of Shares):**	7.00
Employees:	11	**Final Offer Amount ($ Million):**	$84.00
Competitors:	Arena Pharmaceuticals Alizyme plc.	**S-1 Forms:**	**2007 S1-Form download**

- Avoid - Value Gap - Short-Term Growth - Long-Term Growth - Long-Term Value

Company Links

Corporate / History Profile	Executives	Products Ser

Major Stock Holders (Prior To Offering)

Name	
Brian H. Dovey	
Funds affiliated with Domain Associates, L.L.C	
Funds affiliated with Sofinnova Venture Partners VI, L.P	
KPCB Holdings, Inc	
Michael F. Powell, Ph.D	

Business Environment

Obesity is a serious condition that is growing in prevalence and afflicts populations worldwide. In 1980, approxim adult population in the United States was obese, according to the National Health and Nutrition Examination Surv obesity rate had doubled to approximately 30% of the U.S. adult population, according to a later installment of the addition, the survey estimated that another 34% of the U.S. adult population was overweight in 2002.

The growing prevalence of obesity has increasingly been recognized as a significant public health problem. In 2 for Disease Control and Prevention identified obesity as the number one health threat in the United State 300,000 deaths per year in the United States are associated with obesity according to the Department of He Services, or HHS.

Obesity is also a significant health problem outside of the United States. According to the World Health Organizat many as 1.6 billion people worldwide considered to be overweight, of which at least 400 million are estimated to b

Excessive body weight is also associated with various physical complications that are often present and exa obese condition. Diabetes, cancer, hypertension, high cholesterol, coronary artery disease, sleep apnea, live disease, among others, are seen in greater prevalence among the obese than the general population.

In addition, research has established a new disease category called metabolic syndrome, which comprises morbidities, or related conditions, that often accompany obesity. Beyond these consequences, a number involving the CNS may be complicated by obesity. These co-morbidities include anxiety, depression, substanc pain and insomnia. Obesity and its co-morbidities are believed to cause significant added cost to the health care HHS estimated the overall economic costs of obesity in the United States to be $117 billion.

Company Strategy

A biopharmaceutical company focused on the development and commercialization of pharmaceutical products fo of central nervous system, or CNS, disorders, with an initial focus on obesity.

Product/Services Portfolio

The Company is developing Contrave and Excalia for the treatment of obesity. Both product candidates have be combinations of chemical entities that, individually, have already received regulatory approval and have been previously.

Contrave is a fixed dose combination of naltrexone SR and bupropion SR. The Company choses these constitue results of its screening model as well as its understanding of the circuitries in the brain that regulate appetite and

In particular, naltrexone was chosen as a complement to bupropion in order to block compensating mechanism prevent long-term, sustained weight loss. The Company holds the exclusive license to two issued U.S. pate Contrave composition, and it has filed additional patents covering various compositions, methods of use and form

Naltrexone was approved in the United States in 1984 for the treatment of opioid addiction and in 1995 for

alcoholism. In its Contrave clinical trials to date, the Company has used the generic IR formulation of naltrexone.

Bupropion was approved for marketing in the United States in 1985 for depression, marketed under the brand n and in 1997 for smoking cessation, marketed under the brand name Zyban. Bupropion is currently among the prescribed anti-depressants in the United States

Excalia is a fixed dose combination of zonisamide SR and bupropion SR. The combination of zonisamide and l Company's screening model, produced a synergistic increase in POMC neuronal firing, suggesting that this c would enhance satiety and energy expenditure. The Company holds an exclusive license to an issued U.S. pat Excalia composition, and it has filed additional patents covering various compositions, methods of use and formul

Zonisamide IR was approved in the United States in 2000 for the adjunctive treatment of partial seizures, wh epilepsy.

Investment Analysis

Revenue for the nine months ended September 30, 2006 decreased $134,000 as a result of the completion of th collaborative agreement with Eli Lilly as of December 31, 2005.

Research and development expenses increased to $15.4 million for the nine months ended September 30, 2(million for the comparable period during 2005.

General and administrative expenses increased to $3.3 million for the nine months ended September 30, 2(million for the comparable period during 2005.

Interest income increased to $649,000 for the nine months ended September 30, 2006 from $470,000 for th period during 2005.

Income Data (Thousand $ Except EPS)

Year	Revenues	Costs	Oper Income	Taxes	Net Incon
2003	0.00	1,831,041	-1,831,041	0.00	-1,881,0
2004	0.00	7,735,010	-7,735,010	0.00	-7,693,3
2005	262,367	13,095,102	-12,832,735	0.00	-12,088,5
2006	62,451	18,753,999	-18,691,548	0.00	-18,042,6

*As of period ended September 30, 2006

Balance Sheet Data (Thousand $)

Year	Cash	Acct Recv.	Inventory	Total Cur Assets	Total Cur Liability	PPE	Total Assets	LT D
2004	1,674,337	0.00	0.00	1,677,054	358,808	7,618	1,749,672	
2005	8,739,925	0.00	0.00	27,911,935	1,500,247	145,400	28,113,629	
2006	4,984,219	0.00	0.00	11,282,988	2,079,876	120,246	11,876,137	

*As of period ended September 30, 2006

Cash Flow Summary (Thousand $)

Year	Net Cash-Ops	Net Cash-Inv	Net Cash-Fin	
2003	-1,620,929	-11,881	1,651,899	
2004	-7,523,618	-30,000	9,208,866	
2005	-8,715,640	-19,138,860	34,920,088	
2006	-16,103,167	12,343,961	3,500	

*As of period ended September 30, 2006